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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/887,552	06/21/2001	Michael W. Leviten	R-67	5854

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EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	12

DATE MAILED: 12/19/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/887,552	LEVITEN ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communicati n appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) *1-7,9 and 11-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5,6 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group III, claims 8 and 10, in Paper No. 11 is acknowledged.

Claims 1-7, 9, and 11-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Drawings

New corrected drawings are required in this application because of the handwritten corrections in the drawings as originally submitted. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Claim Objections

Claim 10 is objected to for depending from a non-elected claim.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8 and 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse whose genome comprises a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1, wherein said mouse exhibits the following phenotypes as compared to a wild-type mouse: a decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, and a decrease in total time immobile during the tail suspension test, does not reasonably provide enablement for all other transgenic non-human animals embraced by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a transgenic non-human animal comprising a disruption in a cerberus gene and a method of producing a transgenic mouse.

The specification teaches the generation of transgenic mice by disruption of the nucleotide sequence set forth in SEQ ID NO: 1. See pages 6, lines 15-25, and the working examples on pages 50-52 of the specification. The specification teaches that the transgenic mice exhibit the following phenotypes as compared to a wild-type mouse: a decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, and a decrease in total time immobile during the tail suspension test, as a result of a homozygous disruption of the nucleotide sequence set

forth in SEQ ID NO: 1. See pages 50-52 of the specification. While the specification has taught the generation of such a transgenic knockout mouse, the specification has not taught the generation of the other transgenic non-human animals comprising a disruption in a cerberus gene encompassed by the claims. The working examples, guidance and relevant teachings provided by the instant specification are directed to the creation of the above transgenic mouse but do not support the creation of other transgenic non-human animals encompassed by the claims. See pages 50-52.

With regard to claim breadth, the standard under 112, first paragraph entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, in light of the specification, the claimed invention is properly interpreted with regard to the disclosed phenotype of the exemplified transgenic mice comprising a disruption of the nucleotide sequence set forth in SEQ ID NO: 1. Such an interpretation is consistent with the specification despite that the claimed non-human mammals require only that they comprise a disrupted cerberus gene. This is because, with regard to the enablement requirement, one of skill in the art must be provided with both how to make and use the claimed invention. As such, the enabled scope of the claimed invention, in light of the teachings of the specification, is found to be the generation of transgenic mice comprising a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 which exhibit the following phenotypes as compared to a wild-type mouse: a

decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, and a decrease in total time immobile during the tail suspension test.

The following aspect of the rejection under 35 U.S.C. 112, first paragraph is directed to the use of embryonic stem cells to create transgenic knockout non-human animals:

Both the specification and the state of the art have taught that the transgenic knockout technology requires the use of embryonic stem cells that have been genetically manipulated to comprise a disruption in a nucleotide sequence of interest. The specification has not taught creation of a transgenic knockout non-human animal by methods that do not require embryonic stem cells. Presently, the transgenic knockout technology is limited to the mouse system. See below.

With regard to the claim breadth directed to transgenic non-human animals, the specification fails to teach the production of any transgenic non-human animal comprising a disruption in a cerberus gene other than a transgenic knockout comprising a disruption in the nucleotide sequence set forth in SEQ ID NO: 1. It is well known in the knockout art that the production of knockout animals other than mice is undeveloped. This is because ES cell technology is generally limited to the mouse system, at present, and that only "putative" ES cells exist for other species. See Moreadith et al. at page 214, Summary. Seamark (Reproductive Fertility and Development, 1994) supports this observation by reporting that totipotency for ES cell technology in many livestock species has not been demonstrated (page 6, Abstract).

Likewise, Mullins et al. (Journal of Clinical Investigation, 1996) state that "although to date chimeric animals have been generated from several species including the pig, in no species other than the mouse has germline transmission of an ES cell been successfully demonstrated." (page S38, column 1, first paragraph). As the claims are directed to a transgenic non-human animal, which must be generated by the introduction of a transgene into an ES cell or a method of producing a transgenic mouse by introducing a targeting construct into any cell, the state of the art supports that only mouse ES cells were available for use for production of transgenic mice. Also claim 8 as written does not require that the disruption is transmitted through the germline and can be interpreted to read on a mouse comprising a disruption of a cerberus gene in a single cell. Limiting claim 8 to a transgenic mouse whose genome comprises a homozygous disruption of the nucleotide sequence set forth in SEQ ID NO: 1 and claim 10 to an ES cell would be sufficient to overcome this aspect of the rejection. Given the unpredictable state of the art it would have required undue experimentation for the skilled artisan to create transgenic knockout non-human animals of species other than the mouse or to use any cell for creating the same transgenic knockout animals.

Claim 8 encompasses a transgenic non-human animal that comprises a disruption in a cerberus gene that does not exhibit any particular phenotype. The state of the art at the time of filing was such that one of skill could not predict the phenotype of a knockout mouse (Moreadith et al., 1997, J. Mol. Med., Vol. 75, pages 208-216; see page 208, column 2, last full paragraph). Moens et al. (Development, Vol. 119, pages 485-499, 1993) disclose that two mutations produced by homologous recombination in

two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (see abstract). The specification has asserted that the nucleotide sequence set forth in SEQ ID NO: 1 encodes a cerberus family protein. However, it would be difficult to predict any phenotype resulting from disruption of the sequence of SEQ ID NO: 1 in light of the above. The specification discloses that the phenotypes exhibited by knockout mice comprising a homozygous disruption in the nucleotide sequence set forth in SEQ ID NO: 1 are : a decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, and a decrease in total time immobile during the tail suspension test as compared to a wild-type mouse. See pages 50-52 of the specification. Claim 8, as written, does not include a phenotype that differs from the wild-type mouse. Moreover, the skilled artisan would know how to use a transgenic knockout non-human animal that lacks a phenotype, particularly because the instant specification has not provided uses for such; the transgenic mice that have a phenotype of : a decrease in average velocity of movement during open field testing, a decrease in total distance traveled during open field testing, an increase in the number of fecal boli during open field testing, and a decrease in total time immobile during the tail suspension test as compared to a wild-type mouse may be used for drug testing according to the instant specification. The specification overcomes the unpredictability in obtaining a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1; however, the claim is not commensurate in scope with the enabled phenotype disclosed in the specification.

Inclusion of a phenotype associated with a disruption of the nucleotide sequence set forth in SEQ ID NO: 1 in a mouse in the claim would overcome this aspect of the rejection. As discussed above, claim 8 as written can be interpreted to read on a mouse comprising a disruption of a cerberus gene in a single cell, which is unlikely to result in a phenotype different from a wild-type mouse because Cerberus protein is still produced. Given the unpredictable nature of a phenotype that results from disruption of a nucleotide sequence it would have required undue experimentation for the skilled artisan to use a transgenic non-human knockout animal that lacks a phenotype.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic non-human animals comprising a disruption in a cerberus gene, the lack of direction or guidance provided by the specification for the production of transgenic non-human animals comprising a disruption in a cerberus gene, the absence of working examples for the demonstration or correlation to the production of a transgenic knockout non-human animal that exhibits a phenotype other than the exemplified mouse, the unpredictable state of the art with respect to a phenotype that results from disruption of a given nucleotide sequence, the undeveloped art pertaining to the establishment of true embryonic stem (ES) cells of animal species other than mouse, and the breadth of the claims drawn to all non-human animals, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 8 and 10 are rejected under 35 U.S.C. 102(a) as being anticipated by Stanley et al (Genesis, 2000, 26: 259-264; IDS reference—AB).

Stanley teach a transgenic mouse comprising a homozygous disruption the in the cerberus gene. See the abstract and throughout the entire document. Stanley further teach a method for producing a transgenic mouse comprising a homozygous disruption the in the cerberus gene, wherein a targeting construct comprising nucleotide sequences homologous to regions of exon I of the cerberus gene, a hygromycin resistance gene and a gene encoding β-glactosidase was introduced into a mouse embryonic stem cell. The embryonic stem cell was then inserted into a mouse blastocyst to create a transgenic embryo, which was then implanted into a pseudopregnant female, wherein the embryo was allowed to develop to term to generate a chimeric mouse. The chimeric mouse was then bred to homozygosity to generate a transgenic mouse comprising a homozygous disruption of the cerberus gene. See page 260, in the 1st paragraph under the Results section and also see the Methods section: Gene Targeting, beginning on page 261 and bridging to page 262.

Thus, the teachings of Stanley anticipate all of the instant claim limitations.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 8 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Capecchi (1994, Scientific American, pages 52-59) taken with Biben et al (Developmental Biology, 1998, 194: 135-151).

Capecchi teaches knockout technology applied to mice specifically with respect to the disruption of the *Hox*A-3 gene and as the method of producing the same applies to determining the *in vivo* biological function of **any** known gene of interest. See page 59. For example, Capecchi discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning of the gene to the manifestation of disease (See page 54, columns 1-3). Capecchi further discloses the essential components of a targeting vector [(page 54, fig. 1 and page 57, column 1, paragraph 2), such as nucleotide sequences, which are homologous to endogenous genomic nucleotide sequences, that flank a selection marker, such as the neomycin resistance gene] and the steps involved for targeted gene replacement in ES cells as well as in mice (pages 55-56 and diagrams). Capecchi differs from the claimed invention by not teaching transgenic non-human animals and cells that comprise a disrupted cerberus gene.

However, at the time the claimed invention was made, Biben et al teach the cloning of a mouse nucleotide sequence that is a homolog of a *Xenopus* cerberus gene. See the abstract, page 136 column 2 at the bottom, and also the Materials and Methods section beginning on page 146 and bridging to page 147. Biben et al discuss that the mouse Cerberus gene is expressed in the anterior region of the gastrula and somites in the developing mouse embryo. Biben et al goes on to discuss that the similarities in structure, inductive activity, and expression pattern between mouse cerberus and *Xenopus* cerberus suggest a common role in development. Biben et al suggests that inactivation of mouse cerberus by gene targeting will help to delineate its function in head formation in the mouse and the relative roles of primitive endoderm and anterior mesendoderm in this process. See page 146, column 2, in the section entitled mCer-1 in Nascent somites, 2nd paragraph. Note that absent any phenotypic requirements of the claimed transgenic non-human mammal, the combination of the cited prior art is sufficient to make obvious the claimed invention.

Accordingly, in view of the teachings of Biben et al., it would have been obvious for one of ordinary skill in the art, at the time the claimed invention was made, to modify the knockout technology of Capecchi by use of a targeting vector for disruption of the cerberus gene in a mouse with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse as taught by Capecchi et al, and particularly since Biben et al suggest a need to delineate the role of cerberus in head formation in the

mouse and the relative roles of primitive endoderm and anterior mesendoderm in this process. See page 146, column 2, in the section entitled mCer-1 in Nascent somites, 2nd paragraph.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is 703-308-8340. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at 703-305-4051. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center numbers are (703) 308-4242 and (703) 305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (703) 305-3388.

Peter Paras, Jr.

Art Unit 1632

Peter Paras
Art Unit 1632